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Antibody Testing for the AIDS Retrovirus—Implications for Clinicians

A NEW HUMAN RETROVIRUS (variously called LAV, HTLV-III or ARV) has been isolated from tissues of patients with acquired immunodeficiency syndrome (AIDS) and with lymphadenopathy in both Europe and the United States. Antibodies against this virus have been detected in a high percentage of AIDS patients, asymptomatic homosexual men and men with hemophilia. Investigations of blood donors implicated as the source of transfusion-acquired AIDS suggest that there may be a prolonged asymptomatic period of infectivity. Testing of all blood donors for antibody to the AIDS retrovirus (ARV) may soon be required. Enzyme-linked immunosorbent assays (ELISA) for ARV antibody will be used to screen blood units and those found to have the antibody will be discarded. This measure appears both practical and reasonable as a means of preventing future cases of transfusion-acquired AIDS.

The availability of this test will create several problems for practicing clinicians. First, positive tests will be found in persons not in any group known to be at risk for AIDS. Many of these ELISA results will be false-positive. Because confirmatory tests such as Western blotting or immunofluorescence are expensive, technically demanding, not widely available and of uncertain sensitivity, it will be difficult initially to determine which positive results reflect possible infectivity for others or an increased risk of AIDS developing. Despite this uncertainty, persons with repeatedly positive tests should be notified because they can take actions to reduce potential spread of the virus via sexual contact, child bearing or nonsexual transfer of body fluids.

The notification of a positive test result will have enormous emotional impact on most persons and requires that physicians be well informed about the limitations of the tests and implications of the results. Even if systems are developed to inform persons of their results through public agencies, many will seek reassurance and follow-up from their personal physicians.

The second problem for clinicians will be the skillful use of these tests for diagnosis. Because of the wide spectrum of clinical manifestations of AIDS-retrovirus infections and the high prevalence of the AIDS-retrovirus antibody in groups at high risk for AIDS, the diagnostic usefulness of finding the antibody in high-risk patients with unusual clinical syndromes will be limited. For example, should a gay man with idiopathic Bell's palsy or thrombocytopenia and a test positive for AIDS-retrovirus antibody be diagnosed as having an ARV-associated condition? While these tests will help to expand knowledge of the clinical spectrum of AIDS-retrovirus infections, they may also be confusing and misleading.

One possible solution to these problems is the development of tests to detect the AIDS virus directly in blood and tissues. This may be accomplished by growing retroviruses in cultures or detecting virus-specific antigens or nucleic acids. These techniques eventually may replace the soon-to-be released antibody assays. In the meantime, physicians will be faced with the difficult task of explaining and interpreting a test of uncertain significance to anxious patients.

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New Antiarrhythmic Agents—Amiodarone, Mexiletine, Tocainide

UNTIL RECENTLY, antiarrhythmic drug therapy has been restricted to a few agents. Over the past decade, however, there has been a dramatic increase in the number of agents that have been or are soon to be released for clinical use. One drug, tocainide, has just been released for clinical use and two others—amiodarone and mexiletine—are subject to intensive clinical investigation.

Amiodarone

Amiodarone, an agent that prolongs myocardial refractoriness in almost all types of cardiac cells, is quite effective in the clinical management of supraventricular and ventricular arrhythmias and arrhythmias associated with the Wolff-Parkinson-White syndrome. In numerous clinical trials amiodarone effectively suppressed these arrhythmias in patients who did not respond to conventional antiarrhythmic drug therapy. There appears to be general agreement that it requires days, sometimes weeks or even, rarely, months for the full antiarrhythmic efficacy of oral administration of amiodarone to become manifest. There still exists some controversy regarding amiodarone's antiarrhythmic efficacy when given intravenously. The drug is most commonly given orally, usually with a loading dose of 800 to 1,800 mg a day during the first week, followed by a daily maintenance dose of 200 to 800 mg a day. Amiodarone seems to be well tolerated by most patients, but with the increasing use of this drug, several unwanted side effects have been recognized. A small percentage ($\leq 10\%$) of patients have to stop taking amiodarone because of more serious and even life-threatening side effects. These include refractory heart failure; pulmonary fibrosis; central nervous system side effects such as tremor, ataxia, paresthesia, headache and nightmare; sinus arrest, and exacerbation of ventricular tachycardia. Less alarming side effects include corneal microdeposits, with possible association of photophobia, thyroid dysfunction (hypothyroidism or hyperthyroidism), a peculiar bluish or slate-gray discoloration of the skin including the face and abnormalities on liver function tests. These complications may take several weeks or even months to disappear after the drug regimen is discontinued. Many investigators, therefore, have suggested that this drug

be used only in patients with serious arrhythmias unresponsive to routine therapy.

Mexiletine

Mexiletine is a structural analog of lidocaine that, however, is effective given orally. The oral dose ranges from 100 to 400 mg every six to eight hours. For urgent therapy, the intravenous route may be considered, with 200 to 250 mg given over five minutes, followed by an infusion of 60 to 90 mg an hour. Mexiletine is effective in suppressing ventricular arrhythmias; its definite role in the control of these arrhythmias, however, is still not defined. Most of the side effects occur during the initial period of therapy and later disappear in most patients during maintenance therapy. These side effects are frequently of central nervous system origin, including tremor, nystagmus, diplopia, dizziness, dysarthria, paresthesia, ataxia and confusion. Gastrointestinal side effects are common and include nausea, vomiting and dyspepsia. Thrombocytopenia and the presence of antinuclear antibody rarely occur but have been reported in some cases. Side effects are more likely to occur at plasma concentrations of greater than 1.5 to 2 μg per ml, which is very close to the therapeutic level. Cardiovascular effects of mexiletine are infrequent and include hypotension, bradycardia and exacerbation of arrhythmias. Mexiletine is generally well tolerated, however.

Tocainide

Tocainide is another structural analog of lidocaine and is, like mexiletine, effective against ventricular arrhythmias when given orally. Both tocainide and mexiletine have relatively long half-lives (12 hours).

In a number of clinical studies, tocainide has decreased the frequency of ventricular premature depolarizations, with variable side effects on ventricular tachycardia. The precise role of tocainide and the clinical setting in which the drug may eventually be used is still not defined. It would appear that tocainide will exert its antiarrhythmic efficacy at plasma concentrations above 6 μg per ml. The oral dosage regimen for tocainide is usually 400 to 600 mg every eight hours. Tocainide is generally well tolerated. Side effects include central nervous system disorders such as tremor, headache, sweating, altered hearing, dizziness, nervousness, hot flashes, paresthesia, blurred vision or diplopia, anxiety and lightheadedness. Gastrointestinal complaints, however, are more common and include anorexia, vomiting, nausea, abdominal pain and constipation.

These three antiarrhythmic agents hold the potential for dramatically increasing a clinician's ability to control serious cardiac arrhythmias. However, with their use comes the additional problem of serious side effects that must be carefully monitored by the physician.

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Clinical Use of Portable Insulin Pumps

AN ARRAY OF evidence supports the view that diabetic complications are attributable to the metabolic derangements caused by elevated blood glucose levels. This concept has been translated to patient care—thus the increased emphasis on blood glucose control. Ideally, changes in blood glucose levels would automatically be sensed and insulin appropriately released into the portal circulation. This could be accomplished with pancreatic islet cell transplantation or by an implantable glucose-controlled ("closed loop") insulin infusion system, a so-called artificial pancreas. While research into these areas continues, the development of blood glucose self-monitoring and patient-controlled external medication infusion pumps permitted clinical trials and now general clinical use of "open-loop" continuous subcutaneous insulin infusion (CSII) systems.

These insulin infusion devices, which use only short-acting insulin, consist of a syringe or an insulin reservoir in conjunction with a battery-operated pump controlled by an electronic mechanism that is designed for a relatively continuous infusion rate of insulin, the basal rate. This basal rate is supplemented by an increase in the insulin infusion rate controlled manually by the patient at mealtimes, the meal bolus. Patients must regularly—at least three to four times a day—monitor capillary blood glucose responses to the insulin infusion to insure adequate insulin doses. The insulin is delivered through disposable plastic tubing and a subcutaneous needle or catheter that is taped in place for one or two days. The newer pumps have alarms for battery failure, overdelivery and high pressure in the outflow system. The larger and nonprogrammable early pumps have been largely replaced by smaller, often preprogrammable devices that are easily concealed and do not interfere with most daily activities. Multiple basal infusion rates can be used for changing activity levels, and meal bolus injections can be adjusted for variable size, quality and timing of meals. These features provide patients with more freedom in their daily lives.

A policy statement from the American Diabetes Association states the primary indication for CSII:

> Failure to achieve an acceptable level of diabetic control in certain type I diabetic subjects with unusual fluctuations in blood glucose levels, despite intensive efforts with proper diet and multiple injections of insulin in single or mixture form and high patient motivation and compliance.

These guidelines include patients who have hyperglycemia associated with elevated glycosylated hemoglobin or patients with frequent hypoglycemic episodes as a result of trying to maintain blood glucose control. Hyperglycemia during pregnancy has been shown to be a definite risk to the fetus, and CSII in this setting can be especially useful for preventing diabetic complications of pregnancy. Some patients with insulin allergies are sensitive to the protamine or